IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Michael Simons & Youhe Gao
Serial No.	: 09/276,868
Filed	: March 26, 1999
For	: "METHOD FOR PR-39 PEPTIDE REGULATED STIMULATION OF ANGIOGENESIS"
Examiners	: Chih-Min Kam, Christopher Low & Karen C. Carlson
Group art Unit	: 1653
Attorney's Docket No..	: BIS-043

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commission for Patents, Washington, D.C. 20231 on: Aug. 23, 2002.

Attorney for applicants: David Prasilka

Signature: David Prasilka

Date: Aug. 23, 2002

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MARKED UP VERSION OF AMENDED CLAIMS SUBMITTED
PURSUANT TO 37 C.F.R.1.121(c)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants, in fulfillment of and in accordance with the requirements of 37 C.R.F. 121(c)(1)(ii), hereby submit a marked up

version of cancelled claims 1-10 respectively and of amended claims 11-15 respectively.

In addition, in view of the explicit holdings of the U.S. Supreme Court in the *Festo* case recently decided on May 28, 2002 [Festo Corp. v. Shoketsu Kinzoku Kabushiki Co. Ltd. *et al.*, 62 U.S.P.Q.2d 1705 (2002)] concerning the application of the legal doctrine of equivalents to amended claim language, applicants hereby present a formal attestation and affirmation of their legal position and rights: Applicants do not now surrender for any reason, nor have previously surrendered at any time or for any reason during the prosecution of the instant application, any inventive subject matter which is or could be expected to be a particular equivalent of the invention defined by the language of the amended claims then pending by a person ordinarily skilled in this art; and that no presumption of estoppel, either in law or equity, exists or pertains now or at any time previously as a potential bar to the application of the doctrine of equivalence for any and all possible embodiments which may be found to be encompassed now or in the future by the language of the amended claims proffered now or at any time previously for examination to the U.S. Patent Office. Accordingly, applicants affirmatively rebut and explicitly dispute any presumption that the doctrine of equivalence for the language of the amended claims has been surrendered or is not in full force for any reason and

at any time during the prosecution of any and all amended claims prosecuted for the instant application.

The language of cancelled claims 1-10 and of amended claims 11-15 is as follows:

Cancelled: [1. A method for stimulating angiogenesis within a targeted collection of viable cells in-Situ, said method comprising the steps of:

identifying a collection of cells comprising viable cells in-situ as a target for stimulation of angiogenesis;

providing means for effecting an introduction of at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells;

introducing at least one member of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells using said effecting means;

allowing said introduced PR-39 oligopeptide collective member to interact with such proteasomes as are present within the cytoplasm of said targeted collection of cells whereby

(a) the $\alpha 7$ subunit of at least some of the proteasomes interact with said PR-39 oligopeptide collective member, and

(b) the proteolytic degradation of at least one identifiable peptide mediated by said proteasomes with an interacting $\alpha 7$ subunit becomes

markedly inhibited while the proteolytic degradation mediated by said proteasomes with an interacting α7 subunit against other individual peptides remains unaltered, and

(c) the markedly inhibited proteolytic degradation activity of said proteasomes with said interacting α7 subunit results in a stimulation of angiogenesis in-situ.]

Cancelled: [2. A method for altering proteasome-mediated degradation of peptides in-situ within a collection of viable cells, said method comprising the steps of:

identifying a collection of cells comprising viable cells in-situ as a target;

providing means for effecting an introduction of at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells;

introducing at least one member of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells using effecting means;

allowing said introduced PR-39 oligopeptide collective member to interact with such proteasomes as are present within the cytoplasm of said targeted collection of cells whereby

(a) the α7 subunit of at least some of the proteasomes interacts with the PR-39 oligopeptide collective member, and

(b) the proteolytic degradation of at least one identifiable peptide mediated by said proteasomes with an interacting $\alpha 7$ subunit becomes markedly inhibited while the proteolytic degradation mediated by said interacting proteasomes with an interacting $\alpha 7$ subunit against other individual peptides remains unaltered, and

(c) the markedly inhibited proteolytic degradation of the proteasomes with said interacting $\alpha 7$ subunit results in an increased expression of said identifiable peptide in-situ within the targeted collection of cells.**]**

Cancelled: **[**3. The method as recited in claim 1 or 2 wherein said collection of viable cells includes at least one type of cell selected from the group consisting of endothelial cells, myocytes and myoblasts, fibrocytes and fibroblasts, epithelial cells, osteocytes and osteoblasts, neuronal cells and glial cells, erythrocytes, leukocytes, and progenitor cells of all types.**]**

Cancelled: **[**4. The method as recited in claim 1 or 2 wherein said collection of cells comprises at least one tissue selected from the group consisting of myocardium, skeletal muscle, smooth muscle, an artery, a vein, lung, brain, kidney, spleen, liver, gastrointestinal tissue, nerve tissue, limbs, and extremities.**]**

Cancelled: [5. The method as recited in claim 1 or 2 wherein the means for an introduction of a PR-39 oligopeptide collective member include one selected from the group consisting of catheter-based means, injection-based means, infusion-based means, localized intravascular means, liposome-based means, receptor-specific peptide means, and slow releasing means for peptide secretion in living cells and sequestered organisms.]

Cancelled: [6. The method as recited in claim 1 or 2 wherein the means for an introduction of a PR-39 oligopeptide collective member includes DNA sequences coding for at least one PR-39 oligopeptide collective member in an expression vector for transfection and subsequent expression of the PR-39 oligopeptide collective member within said cells.]

Cancelled: [7. The method as recited in claim 1 or 2 wherein said method is practiced under in-vivo conditions.]

Cancelled: [8. The method as recited in claim 1 or 2 wherein said method is practiced under in-vitro conditions.]

Cancelled: [9. The method as recited in claim 1 or 2 wherein degradation of IκBα is inhibited.]

Cancelled: [10. The method as recited in claim 1 or 2 wherein degradation of HIF- 1α is inhibited.]

11 (Thrice Amended). A [family of] PR-39 derived oligopeptide family [oligopeptides] whose members individually cause a selective [an] inhibition of proteasome-mediated degradation of at least one specific [identifiable] peptide in-situ after introduction intracellularly to a viable cell, each member of said PR-39 derived oligopeptide family being

less than 26 amino acid residues in length;

an oligopeptide whose N-terminal amino acid residue sequence [which] begins with Arg-Arg-Arg;

an analog of [at least partially homologous with] the amino acid sequence of native PR-39 peptide;

pharmacologically active for [markedly] altering the proteolytic degradation activity of proteasomes in-situ;

able to interact in-situ with at least the α7 subunit of such proteasomes as are present within the cytoplasm of the cell; and

able selectively to alter the proteolytic degradation activity of said proteasomes having an interacting α7 subunit such that the proteolytic degradation mediated by said proteasomes against at least one specific [identifiable] peptide becomes [markedly] inhibited while the proteolytic degradation mediated by said proteasomes against other [individual]

peptides remains unaltered.

12 (Thrice Amended). The PR-39 derived oligopeptide family as recited in claim 11 or 15 whose membership includes a peptide comprised of 15 amino acid residues whose sequence is Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr-Leu-Pro-Arg-Pro-Arg-Pro-Pro **[[]** (SEQ ID NO; 3) **[]]**.

13 (Thrice Amended). The PR-39 derived oligopeptide family as recited in claim 11 or 15 whose membership includes a peptide comprised of 11 amino acid residues whose sequence is Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr-Leu-Pro-Arg **[[]** (SEQ ID NO: 4) **[]]**.

14 (Thrice Amended). The PR-39 derived oligopeptide family as recited in claim 11 or 15 whose membership includes a peptide comprised of 8 amino acid residues whose sequence is Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr **[[]** (SEQ ID NO: 5) **[]]**.

15 (Twice Amended). A **[**family of**]** PR-39 derived <u>oligopeptide family</u> **[**oligopeptides**]** whose members cause <u>a selective</u> **[**an**]** inhibition of protease-mediated degradation of at least one <u>specific</u> **[**identifiable**]** peptide in-situ after introduction intracellularly to a viable cell, each member of said oligopeptide family being:

less than 20 amino acid residues in length;

an oligopeptide whose N-terminal amino acid residue sequence begins with Arg-Arg-Arg;

an analog of [at least partially homologous with] the amino acid sequence of native PR-39 peptide;

pharmacologically active for [markedly] altering the proteolytic degradation activity of proteasomes in-situ;

able to interact in-situ with at least the α7 subunit of such proteasomes as are present within the cytoplasm of the cell; and

able selectively to alter the proteolytic degradation activity of said proteasomes having an interacting α7 subunit such that the proteolytic degradation mediated by said proteasomes against at least one specific [identifiable] peptide becomes [markedly] inhibited while the proteolytic degradation mediated by said proteasomes against other [individual] peptides remains unaltered.

Respectfully submitted

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Aug. 23, 2002

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